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Review: stimulants improve overt and covert aggression related behaviours in attention deficit hyperactivity disorder

Connor DF, Glatt SJ, Lopez ID, et al. ***Psychopharmacology and aggression. I: A meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD.*** *J Am Acad Child Adolesc Psychiatry 2002 Mar;**41**:253–61.*

QUESTION: In children with attention deficit hyperactivity disorder (ADHD), are stimulants more effective than placebo for improving overt and covert aggression related behaviours?

Data sources

Studies were identified by searching Medline (1970–2001) and by reviewing bibliographies of relevant articles.

Study selection

Studies in English language were selected if they were controlled trials (crossover or parallel groups) comparing stimulants with placebo, were published in peer reviewed scientific journals, reported quantitative data on independent effects for aggression related behaviours, used a rating scale or method of observation to assess aggression related behaviours, and included children or youth (mean age <18 y) with ADHD. Reports that only included effects of stimulants on the core symptoms of ADHD were excluded.

Data extraction

Data were extracted on sample size, demographical characteristics, comorbid psychiatric disorder, key components of the intervention, duration of treatment, study quality, and outcomes. Outcomes included overt (resulting in a direct confrontation with others) and covert (hidden from others) aggression related behaviours.

Main results

28 studies (n=683) met the selection criteria. Stimulant types included methylphenidate (21 studies), dextroamphetamine (5 studies), and pemoline (2 studies). Reduction in clinician, parent, teacher, and overall ratings of overt aggression was greater in the stimulant than in the placebo group (table). Reduction in clinician and overall ratings of covert aggression was greater in the stimulant than in the placebo group (table). Overall stimulant effect sizes for overt aggression were negatively correlated with the prevalence of conduct disorder (correlation coefficient [r] $=-0.508$, $p<0.05$), or oppositional defiant disorder ($r=-0.613$, $p<0.05$). However, stimulant effect sizes for covert aggression (clinician ratings) were positively correlated with the prevalence of conduct disorder (r 0.884, $p<0.05$).

Conclusion

In children with attention deficit hyperactivity disorder, stimulants are more effective than placebo for improving overt and covert aggression related behaviours.

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For correspondence: Dr D F Connor, University of Massachusetts Medical School, Worcester, MA, USA. ConnoD01@ummhc.org

*Stimulants v placebo for aggression related behaviours in attention deficit hyperactivity disorder at 1–42 days**

Outcomes	Number of studies (n)	Mean effect size (95% CI)	Percentage of patients with worse outcome†
Overt aggression			
Clinician ratings	18 (367)	0.76 (0.63 to 0.88)	78% (74 to 81)
Parent ratings	13 (381)	0.78 (0.42 to 1.14)	78% (66 to 87)
Teacher ratings	16 (414)	1.06 (0.79 to 1.32)	86% (79 to 91)
Overall ratings	28 (683)	0.86 (0.70 to 1.02)	81% (76 to 85)
Covert aggression			
Clinician ratings	6 (100)	0.83 (0.20 to 1.46)	80% (58 to 93)
Overall ratings	7 (131)	0.75 (0.21 to 1.29)	77% (58 to 90)

*CI defined in glossary.
†Percentage of patients in the control group with a worse outcome than the average patient in the treatment group; see glossary.

COMMENTARY

The meta-analysis by Connor *et al* puts to rest a long standing assumption that aggressive behaviour is not affected by treatment with stimulants in children with ADHD. 28 studies meeting the stipulated methodological criteria, including systematic ratings of aggressive behaviour and use of placebo controls, were included in the meta-analysis. In each of these studies, the results favoured treatment with stimulants. When results are highly consistent, meta-analysis will not reveal therapeutic findings obscured by design problems, such as small samples. Individually, small studies may not yield significant treatment differences between drug and placebo, but their aggregate results might point to effects that had gone undetected. Given the unanimity in findings, what can we learn from this meta-analysis? The authors generated effect sizes for treatment with stimulants, but how good are they? Estimating effect sizes is tricky because it depends on the initial characteristics of the children enrolled in each of the studies — in this instance how aggressive they were, the measures used to assess aggression, and the type of informant (eg, parent, teacher, and clinician). The authors combined data from these informants to generate an overall estimate of the effect size for treatment with stimulants. That seems like a reasonable approach. Yet, it is clear that parents report the least improvement in children treated with stimulants, relative to placebo, and teachers regularly indicate the greatest gains in the treated group. Given the complex interpersonal histories between aggressive children and their parents, it is not clear what is attained when parental and teacher ratings are combined. Also, doses vary widely across studies. For example, the daily dosage of methylphenidate, the most studied stimulant, ranges from 7.5–60 mg/day. Can we assume that these regimens represent equivalent treatments? I doubt it. The duration of studies also varies widely: from 1–42 days. One wonders whether short durations provide meaningful clinical information about the treatment of a chronic disorder. Of course, the authors of the meta-analysis cannot be faulted for these dilemmas. The findings are all the more convincing because they occur despite the great variation in dosage and periods of observation. However, children who are aggressive in the context of having ADHD or conduct disorder require long term treatment. Unfortunately, the studies that make up the meta-analysis do not report on the value of treatment with stimulants over the long term. Without such information, there is no bandwagon to jump on.

Rachel G Klein, PhD
New York University School of Medicine
New York, New York, USA